REMARKS

Claims 1-5, 29-36, 40-52 and 54-59 are pending in the above-identified application. Of the pending claims, Claims 54, 58 and 59 are allowed. Claims 1-5, 29-36, 40-52 and 55-57 are rejected under 35 U.S.C. §102, as discussed below. No amendments have been made by way of this response. Reconsideration of Claims 1-5, 29-36, 40-52 and 55-57 is respectfully requested.

Rejection of Claims Under 35 U.S.C. §102

The rejection of Claims 1-5, 29-36, 38-52 and 55-57 was maintained under 35 U.S.C. §102(b) as allegedly being anticipated by Zajac *et al.* (1997. *Int J Cancer* 71:491-496, hereinafter referred to as "Zajac"), Kittlesen *et al.* (1998. *J Immunol* 160:2099-2106, hereinafter referred to as "Kittlesen"), or Jager *et al.* (1998. *J Exp Med* 187:265-270, hereinafter referred to as "Jager").

The Examiner previously asserted that while the number of cells in a sample taught by Zajac, Kittlesen or Jager may be a low number, there is no reason why such a low number could not be adoptively administered. In the response filed February 28, 2008, the claims were amended to recite, in relevant part, a composition comprising a sufficient number of a first isolated T cell to be suitable as an adoptive immunotherapeutic, which Applicants presume to have addressed the Examiner's previous ground for the rejection.

The Examiner now asserts in the instant Office Action that Applicants used the recitation that the T cells be suitable "as an adoptive immunotherapeutic" to disqualify the prior art by allegedly arguing that cells taught by the reference are obtained from a cancer patient and thus would not suitable for use as an immunotherapeutic. The Examiner argues that cells from a cancer patient would be "suitable" for autologous immunotherapy, and therefore, maintained the rejection. Regarding this new basis for the rejection of the claims, Applicants respectfully note that the fact that the cells were obtained from a cancer patient was not the basis Applicant's argued to disqualify the art. Applicants do **not** concede that the cell preparations from cancer patients described in the reference would be suitable for autologous immunotherapy, but have not presented remarks regarding this new basis for rejection. Instead, Applicants maintain that the cited references do not anticipate the pending claims for the reasons already of record as re-iterated below—namely, the compositions taught by the reference are not suitable "as adoptive

immunotherapeutics" because they contain agents that are unacceptable for administration to a human.

The Law of Anticipation

Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). More particularly, a finding of anticipation requires the disclosure in a single piece of prior art of **each and every** limitation of a claimed invention. *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 34 F.3d 1048, 1052 (Fed. Cir. 1994). "To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." *Brown v. 3M*, 265 F.3d 1349 (Fed. Cir. 2001).

The Claims

The claims relate to compositions that comprise a sufficient number of a T cell to be suitable as an adoptive immunotherapeutic. The claimed compositions comprise a first isolated T cell expressing a T cell receptor specific for an MHC-peptide complex containing a housekeeping epitope. In some embodiments, the claimed compositions further comprise a second isolated T cell population, wherein the first and second T cell populations recognize two different housekeeping epitopes. Accordingly, Claim 1 recites a composition comprising a sufficient number of a first isolated T cell to be suitable as an adoptive immunotherapeutic. Claims 2-5, 29-36 and 40-41 depend from independent Claim 1 and thus contain all the features thereof as well as additional features recited within the claims. Claim 42 recites a composition comprising at least a first and a second isolated T cell population, wherein said first population comprises a sufficient number of a first T cell to be suitable as an adoptive immunotherapeutic for an animal, and wherein said second population comprises a sufficient number of a second T cell to be suitable as an adoptive immunotherapeutic for an animal. Claims 43-52 and 55-57 depend from independent Claim 42 and thus contain all the features thereof as well as additional features recited within the claims.

Zajac Does Not Anticipate the Claims

The rejection of claims 1-5, 29, 30, 33-35, 38-52 and 55-57 was maintained under 35 U.S.C. §102(b) as allegedly being anticipated by Zajac *et al.* (1997. *Int J Cancer* 71:491-496, hereinafter referred to as "Zajac"). On page 3 of the Office Action, it was asserted that Applicants used the recitation that the T cells be suitable "as an adoptive immunotherapeutic" to disqualify the prior art by allegedly arguing that cells taught by the reference are obtained from a cancer patient and thus would not suitable for use as an immunotherapeutic. The Examiner then argued that cells from a cancer patient would be "suitable" for autologous immunotherapy, and therefore, maintained the rejection. As noted above, Applicants do **not** concede that the cell preparations from cancer patients described in the reference would be suitable for autologous immunotherapy, but have not presented remarks regarding this basis for rejection. Instead, Applicants maintain that the cited references do not anticipate the pending claims for the reasons already of record as re-iterated below—namely, the compositions taught by the reference are not suitable "as adoptive immunotherapeutics" because they contain agents that are unacceptable for administration to a human.

As an initial matter, Claims 38 and 39 were previously cancelled without prejudice. Accordingly, the rejection of these claims is considered moot.

As previously argued, Zajac discloses generation of tumoricidal lymphocytes from healthy donors after *in vitro* stimulation with a replication-incompetent *Vaccinia* virus encoding MART-1/Melan-A 27-35 epitope. However, Zajac does not teach compositions that are suitable as an adoptive immunotherapeutic. As previously argued, and as discussed and acknowledged during the interview, the T cells ultimately derived and disclosed by Zajac are not suitable for adoptive administration to a human because, during generation of MART-1/Melan-A_{27-35}-specific CTLs, the T cells are exposed to agents which are then present in the compositions, thus rendering the compositions unsuitable for adoptive administration to a human. For example, the compositions used in generating MART-1/Melan-A_{27-35}-specific CTLs by Zajac contain antibiotics and recombinant human IL-2, the presence of either of which renders the compositions unsuitable for administration to a human. Such agents are unacceptable as components of a composition to be administered to a human or an animal due to expected toxicity and/or allergic reactions in response to such agents. Thus, contrary to the Patent

Office's assertions, Applicants argued that it is the exposure of T cells to such agents during *ex vivo* manipulation that renders such cells unsuitable for use as an immunotherapeutic. Thus, the compositions disclosed in Zajac would not be suitable as an immunotherapeutic even for autologous administration where the donor is an intended recipient. For at least these reasons, the disclosed compositions are also not suitable for adoptive administration to an animal.

In addition, the initial T cell populations disclosed in Zajac do not exhibit any detectable reactivity against the MART-1/Melan-A_{27-35} peptide. Thus, Zajac does not teach that TILs obtained from a melanoma patient include any number, let alone a sufficient number, of a first T cell to be suitable as an adoptive immunotherapeutic.

Moreover, as discussed in the response filed March 5, 2007, the subject matter of Claims 42-52 and 55-57 relates to a composition comprising at least a first and a second isolated T cell population, wherein the first and second T cell populations recognize two different housekeeping epitopes. Independent Claim 42 recites that the T cell populations expresses a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope, and that housekeeping epitopes of the first T cell population is not the same as the housekeeping epitope for the second T cell population. Thus, the T cell populations recited in Claim 42 exhibit specificity for two distinct housekeeping epitopes.

In stark contrast to the subject matter of Claims 42-52 and 55-57, the cited reference discloses a T cell population that exhibits cytotoxic activity specific for a single epitope, MART-1/Melan-A_{27-35} (*see*, Zajac *et al.* at, for example, page 493, col. 1). At no point does Zajac teach or suggest a composition comprising at least two isolated T cell populations wherein the T cell populations exhibit cytotoxic activity specific for two different housekeeping epitopes.

For at least the reasons discussed above, Zajac does not teach each and every feature of the claims. Accordingly, Applicants respectfully submit that the reference does not anticipate the claims. Withdrawal of the rejection is requested.

Kittlesen Does Not Anticipate the Claims

The rejection of claims 1-5, 29, 30, 33, 34, 36 and 38-41 was maintained under 35 U.S.C. §102(b) as allegedly being anticipated by Kittlesen *et al.* (1998. *J Immunol* 160:2099-2106, hereinafter referred to as "Kittlesen"). On page 5 of the Office Action, it was asserted that

Applicants used the recitation that the T cells be suitable "as an adoptive immunotherapeutic" to disqualify the prior art by allegedly arguing that cells taught by the reference are obtained from a cancer patient and thus would not suitable for use as an immunotherapeutic. The Examiner then argued that cells from a cancer patient would be "suitable" for autologous immunotherapy, and therefore, maintained the rejection.

As an initial matter, Claims 38 and 39 were previously cancelled without prejudice. Accordingly, the rejection of these claims is considered moot.

As previously argued, Kittlesen teaches recognition by human melanoma patients of an HLA-A1-restricted epitope from tyrosinase containing two cysteine residues. However, Kittlesen discloses that CTLs derived from peripheral blood lymphocytes, tumor-involved nodes, or tumor-draining nodes are cultured *in vitro* and repeatedly stimulated with autologous tumor cells. The cells are cultured in medium with fetal calf serum, glutamine and antibiotics, and the presence of such components in the medium renders the disclosed compositions unsuitable for adoptive administration to a human and therefore unsuitable as an adoptive immunotherapeutic. Thus, contrary to the Patent Office's assertions, Applicants argued that it is the presence of certain components in the medium during *ex vivo* manipulation taught by the cited reference that renders the composition disclosed in Kittlesen unsuitable for use as an immunotherapeutic. Thus, the compositions disclosed therein would not be suitable as an immunotherapeutic even for autologous administration where the donor is an intended recipient. Additionally, no tyrosinase-reactivity is reported for T cells directly obtained from a melanoma patient. Thus, the disclosed compositions do not include a sufficient number of a first T cell to be suitable as an adoptive immunotherapeutic.

In view of the foregoing, Kittlesen does not teach and every feature of the claims. Accordingly, Applicants respectfully submit that the reference does not anticipate the claims. Withdrawal of the rejection is requested.

Jager Does Not Anticipate the Claims

The rejection of claims 1-5, 29-32, 35 and 38-41 was maintained under 35 U.S.C. §102(b) as allegedly being anticipated by Jager *et al.* (1998. *J Exp Med* 187:265-270, hereinafter referred to as "Jager"). On page 6 of the Office Action, it was asserted that Applicants used the

recitation that the T cells be suitable "as an adoptive immunotherapeutic" to disqualify the prior art by allegedly arguing that cells taught by the reference are obtained from a cancer patient and thus would not suitable for use as an immunotherapeutic. The Examiner then argued that cells from a cancer patient would be "suitable" for autologous immunotherapy, and therefore, maintained the rejection. Applicants maintain that the cited reference does not anticipate the claims.

As an initial matter, Claims 38 and 39 were previously cancelled without prejudice. Accordingly, the rejection of these claims is considered moot.

As previously argued, Jager teaches the antigen-specific humoral and cellular immune responses against human tumor antigens. However, to obtain the stable CTL line NW38-IVS-1, Jager cultured mixed lymphocyte tumor cell cultures of peripheral blood lymphocytes (PBLs) and the autologous tumor cell line from patient NW38 in medium containing antibiotics. The presence of antibiotics in the medium used to culture CTLs renders the CTL composition unsuitable for adoptive administration to a human and therefore unsuitable as an adoptive immunotherapeutic. Thus, contrary to the Patent Office's assertions, Applicants argued that it is the presence of certain components in the medium during *ex vivo* manipulation taught by the cited reference that renders the composition disclosed in Jager unsuitable for use as an immunotherapeutic. Thus, the compositions disclosed therein would not be suitable as an immunotherapeutic even for autologous administration where the donor is an intended recipient.

Furthermore, Jager discloses that the needle biopsy obtained from a melanoma patient was used to establish the tumor cell line NW-MEL-38; such cells are clearly tumor cells, not reactive T cells. Jager only discloses NY-ESO-1 reactive T cells after mixed lymphocyte tumor cell cultures of PBLs and NW-MEL-38. Thus, Jager does not teach that PBLs obtained from a melanoma patient include any number, let alone a sufficient number, of a first T cell to be suitable as adoptive immunotherapeutic.

In view of the foregoing, Jager does not teach each and every feature of the claims. Accordingly, Applicants respectfully submit that the reference does not anticipate the claims. Withdrawal of the rejection is requested.

Allowable Subject Matter: Allowed Claims 54, 58 and 59

Claims 54, 58 and 59 are allowed.

Conclusion

Applicants submit that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact Applicants' representative at the number provided below in order to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 04-0258.

Respectfully submitted,

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